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EXAMINER	
KISHORE, GOLLAMUDI S	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/667,931	HUI ET AL.	
	Examiner	Art Unit	
	GOLLAMUDI S. KISHORE	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *87-119* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2-22-10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 2-16-10 is acknowledged.

Claims included in the prosecution are 87-119.

Claim Rejections - 35 USC § 112

1. Claims 87-117 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants amend claim 87 to recite the limitation "purified phospholipids". This term does not appear to have support in the specification as originally filed and therefore, deemed to be new matter.

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 87-117 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

'purified' renders claim 87 indefinite since the percentage of purification is unclear.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 87-111 and 117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg ((5,677,472) in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination.

Nyberg et al. disclose methods of preparing phospholipids precipitates comprising mixing a phospholipids blend containing phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin in an organic solvent mixture of polar organic solvent (e.g. methanol) and essential non-polar organic solvent (e.g. toluene), concentrating the solution, then add a second organic solvent of intermediate polarity (e.g. acetone and heptane) to cause precipitation of phospholipids at about 13°-25° C, and drying the precipitate (see example 1, 2, 6, and claim 1). The concentration of sphingomyelins in the solvent is 2-20 mg/ml (column 6, lines 44-48). Nyberg et al. specifically indicate separation of phospholipids into different phases (column 5, lines 53-57; example 1, lines 56-67; and example 2).

Nyberg et al and Unger teach steps a, b and c. What is lacking in Nyberg is the teaching of the preparation of lipid suspensions or liposomes using the lipids of Nyberg et al and Unger (steps d and e).

Kissel teaches a method of preparation of liposomes (lipid suspension). The method involves dissolving the phospholipid (lecithin) in methylene chloride and adding an aqueous solution of a biologically active agent, IL-2 (Example B1 on col. 13). The lipids taught include phosphatidylcholines and sphingomyelin (col. 3, lines 1-51).

Similarly Papahadjopoulos teaches a method of preparation of liposomes wherein the phospholipids are dissolved in diethyl ether and adding an aqueous solution of the active agent (example 4 and claims). Various phospholipids could be used (columns 4 and 5).

Lenk similarly teaches a method of preparation of liposomes wherein the phospholipids are dissolved in an organic solvent and adding an aqueous medium (examples and claims). The lipids used include sphingomyelin (col. 7).

Kikuchi teaches a method of preparation of liposomes wherein heated propylene glycol containing lecithin or DPPC is added with an aqueous solution. Other solvent taught is polyethylene glycol. Kikuchi further teaches sizing the liposomes using polycarbonate filters (col. 3, lines 33-46; examples and claims).

It would have been obvious to one of ordinary skill in the art, if lipid encapsulation of an active agent is desired, to use the steps taught by Kissel or Papahadjopoulos or Lenk to prepare liposomes since it is an art known method of preparing liposomes. Although the references do not teach all of the non-aqueous solvents such as propylene glycol and their amounts, since the principle of precipitation is the same and since Nyberg teaches the use of suitable solvent systems (col. 3, lines 6-1 and col. 9, lines 54-57), in the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to use any solvent which is suitable with a reasonable expectation of success. Similarly, since the purpose is to dissolve the lipids in a solvent, it would have been obvious to one of ordinary skill in the art to use suitable temperatures to achieve the complete dissolution of the phospholipids. Applicant's claim limitation of sterilizing

filter in claim 107 is noted. However, Kikuchi teaches the filtration of the liposomes using filters and this process results in sterilization. The examiner cites in this context, the reference of Papahadjopoulos (6,210,707) which teaches liposomal suspensions are sterilized when filtered through a conventional filter (see col. 17, lines 35-44).

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues the following:

"With respect to issues raised in the remainder of the rejection, Applicant has amended claim 87 to clarify that the process as claimed includes contacting at least two separate, individual lipids with a first non-aqueous solvent that causes the lipids to dissolve and form a lipid solution. The contacting of the phospholipids with the non-aqueous solvent may include mixing separate phospholipids together and then contacting with the first non-aqueous solvent or may include adding separate phospholipids sequentially to the first non-aqueous solvent. The Examiner concludes at page 2 of the Office Action that Nyberg et al. teaches steps a, b, and c of claim 87. Applicant respectfully disagrees. The steps of claim 87 include contacting at least two purified phospholipids with a first non-aqueous solution to dissolve the phospholipids into a blended solution. The contact can be either adding each of the at least two phospholipids sequentially to the first non-aqueous solvent, or mixing the at least two phospholipids together and then adding the mixture to the first non-aqueous solvent to make a blended solution. The additional steps include contacting the blended solution with a second non-aqueous solution to precipitate the blended phospholipids, contacting the blended phospholipids with a third non-aqueous solvent to dissolve the phospholipids into a lipid blend solution, and contacting the lipid blend solution with an aqueous solution to yield a lipid suspension. Each step is important to permit preparation of the uniform phospholipid blend of the claimed invention, which reduces difficulties encountered with using alternative methods. Past difficulties have included lack of uniformity, lack of purity, difficulty in recovery of solids, etc. (see page 2 of specification as filed.) The Examiner states at page 2: Nyberg et al. disclose methods of preparing phospholipids precipitates comprising mixing a phospholipids blend containing phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin in an organic solvent mixture of polar

organic solvent (e.g. methanol and essential non-polar organic solvent (e.g. toluene), concentrating the solution, then add a second organic solvent of intermediate polarity (e.g. acetone and heptane) to cause precipitation of phospholipids at about 13°C-25°C, and drying the precipitate (see example 1, 2, 6, and claim 1). As indicated by the Examiner in this quote, Nyberg starts with a mixture of phospholipids that is mixed with an organic solvent mixture to precipitate out the phospholipids. Nyberg does not teach or suggest starting with individual, separate, purified, phospholipids and does not teach adding each of the individual phospholipids sequentially to a first non-aqueous solvent or mixing each of the individual phospholipids together and then adding them to a non-aqueous solvent. The claims as amended are drawn to preparing a blend of at least two individual phospholipids and contacting the blend with a series of solvents to permit preparation of a uniform blend of phospholipids followed by use of that uniform blend to prepare a lipid suspension. Each step in claim 87, as amended, is important for the outcome of the process. Contacting at least two purified phospholipids with a first non-aqueous solution to dissolve the phospholipids into a blended solution. The contact can be either adding each of the at least two phospholipids sequentially to the first non-aqueous solvent, or mixing the at least two phospholipids together and then adding the mixture to the first non-aqueous solvent to make a blended solution. The additional steps include contacting the blended solution with a second non-aqueous solution to precipitate the blended phospholipids, contacting the blended phospholipids with a third non-aqueous solvent to dissolve the phospholipids into a lipid blend solution, and contacting the lipid blend solution with an aqueous solution to yield a lipid suspension. Each step is important to permit preparation of the uniform phospholipid blend of the claimed invention, which reduces difficulties encountered with using alternative methods. Past difficulties have included lack of uniformity, lack of purity, difficulty in recovery of solids, etc. (see page 2 of specification as filed.) The Examiner states at page 2: Nyberg et al. disclose methods of preparing phospholipids precipitates comprising mixing a phospholipids blend containing phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin in an organic solvent mixture of polar organic solvent (e.g. methanol and essential non-polar organic solvent (e.g. toluene), concentrating the solution, then add a second organic solvent of intermediate polarity (e.g. acetone and heptane) to cause precipitation of phospholipids at about 13°C-25°C, and drying the precipitate (see example 1, 2, 6, and

claim 1). As indicated by the Examiner in this quote, Nyberg starts with a mixture of phospholipids that is mixed with an organic solvent mixture to precipitate out the phospholipids. Nyberg does not teach or suggest starting with individual, separate, purified, phospholipids and does not teach adding each of the individual phospholipids sequentially to a first non-aqueous solvent or mixing each of the individual phospholipids together and then adding them to a non-aqueous solvent. The claims as amended are drawn to preparing a blend of at least two individual phospholipids and contacting the blend with a series of solvents to permit preparation of a uniform blend of phospholipids followed by use of that uniform blend to prepare a lipid suspension. Each step in claim 87, as amended, is important for the outcome of the process. The Examiner states at page 4 of the Office Action that Nyberg's starting mixture contains "three individual phospholipids." Applicant submits that it is erroneous to interpret a "mixture" of lipids to mean three individual lipids. As described above, the at least two individual lipids in the claimed invention are separate lipids that are mixed together as part of the preparation process, a step that is clearly different than, and not taught or suggested by, Nyberg et al. Applicant submits that Nyberg does not teach any individual phospholipids, but clearly begins with a combination of phospholipids with the stated goal of separating out the phospholipids. One of ordinary skill in the art would not use the methods of Nyberg's separation to make the claimed invention when the claimed invention encompasses the opposite process, that of making a uniform blend of two or more previously separate phospholipids. The amendment of claim 87 further clarifies that the phospholipids of the instant claims are separate, individual purified phospholipids that are combined in a step of the claimed process. In contrast, Nyberg et al. teaches separating out lipids from naturally occurring mixtures. Nyberg teaches a starting material that is a "phospholipids blend" that is exposed to solutions to separates out the phospholipids from the mixture for further use. Nyberg et al. fails to teach or suggest mixing together individual, separate phospholipids to make a lipid blend and therefore, at a minimum, fails to teach step (a), an element of claim 87."

These arguments are not persuasive. First of all, whether a phospholipid mixture of two phospholipids is first dissolved in a first solvent, precitipated with another solvent and again dissolved in another solvent to form a solution or the purified phospholipid mixture is dissolved in a solvent in one

step, the ultimate product will be a lipid solution and it is unclear to the examiner as to how the product can be different. Applicant has not shown that the two products will be different.

Applicant's arguments that the secondary references do not teach combining at least two phospholipids and contacting the phospholipid mixture with three non-aqueous solutions followed by an aqueous solution as set forth in claim 87 are not persuasive. Kessel teaches a mixture of lecithin and phosphatidylserine in t-butanol and mixing this solution with an aqueous solution. As pointed out above, irrespective of how many times the mixture is precipitated, when it is finally dissolved in a non-aqueous solvent, the phospholipid mixture would be the same in a dissolved state compared to two phospholipids added directly to a non-aqueous solvent so as to dissolve them. Kessel, Papahadjopoulos, Lenk and Kikuchi (which have similar teachings) are combined for their teachings of combining the non-aqueous solvent containing phospholipids to an aqueous solvent to form lipid suspension. As pointed out before, instant claims do not recite any specific amounts of individual phospholipids and therefore, the reference still meets the requirements of instant steps a to c. The examiner also points out that Nyberg also teaches the knowledge in the art of the use of phospholipids in the preparation of liposomes (col. 1, lines 18-30).

Applicant's arguments that Kissel, Papahadjopoulos, Kikuchi and Lenk do not teach the missing elements of the claims as amended and that these references do not teach lipid blend prior to liposome preparation are not persuasive since these references clearly teach that either single phospholipids or mixtures of phospholipids are routinely used in the preparation of liposomes. These references show the use of pure phospholipids in the preparation of liposomes and applicant has not shown any

unexpected results resulting from the use of an additional precipitation step by direct comparison using the pure phospholipids taught by Kissel, Papahadjopoulos, Kikuchi and Lenk.

3. Claims 111-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg ((5,677,472) in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination, further in view of Swaerd-Nordmo (6,165,442).

The teachings of Nyberg, Unger, Kissel, Kikuchi, Papahadjopoulos and Lenk have been discussed above. These references do not teach how to prepare liposomes containing ultrasound contrast agents containing perfluoropropane, that is, exchange air with perfluorohydrocarbons in a vacuum chamber.

Swaerd-Nordmo while disclosing vesicular preparations containing contrast agents teaches that the contrast agents can be incorporated by the exchanging perfluoropropane in a vacuum chamber (col. 3, Example 1). Various phospholipids which could be used are taught on col. 3, line 60 through col. 4, line 28).

It would have been obvious to one of ordinary skill in the art to use the method of Swaerd-Nordmo to encapsulate perfluoropropane in the teachings of the primary references if the intended purpose is to use the liposomes for the delivery of ultrasound contrast agents since such a method is known in the art as taught by Swaerd-Nordmo.

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Nyberg, Kissel, Papahadjopoulos, Kikuchi and Lenk. Applicant argues that Swaerd-Nordmo fails to

teach or suggest methods to make a lipid blend as claimed. The examiner points out that this reference is combined for its teachings of encapsulating ultrasound contrast agents; steps a-c are obvious over the combination of Nyberg with the secondary references.

4. Claim 115-116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg ((5,677,472) in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination, in view of Swaerd-Nordmo, further in view of Unger (6,071,495).

The teachings of Nyberg, Unger, Kissel, Papahadjopoulos, Lenk, Kikuchi and Swaerd-Nordmo have been discussed above. What is lacking in these references is the final sterilization of the product. Such a sterilization however, would have been obvious to one of ordinary skill in the art if the preparation is used for human administration especially by an injection mode since sterilization of contrast agent containing liposomes by gamma-ray irradiation is known in the art as taught by Unger 6,071,495) (see col. 17, line 42 through col. 18, line 14).

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Nyberg, Kissel, Papahadjopoulos, Kikuchi and Lenk. Applicant argues that Unger fails to teach or suggest methods to make a lipid blend as claimed. The examiner points out that this reference is combined for its teachings of sterilization; steps a-c are obvious over the combination of Nyberg with the secondary references.

5. Claim 117 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg ((5,677,472) in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination, further in view of Unger 6,416,740.

The teachings of Nyberg, Kissel, Papahadjopoulos and Lenk have been discussed above. What is lacking in these references is the use of claimed lipid combination (DPPA, DPPE- PEG5000, and DPPC) in the preparation of the liposomes.

Such a use however, would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Unger shows that this lipid combination is routinely used for the preparation of lipospheres (examples 3 and 12).
Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Nyberg, Kissel, Papahadjopoulos and Lenk. Applicant argues that Unger fails to teach or suggest methods to make a lipid blend as claimed. The examiner points out that this reference is combined for its teachings of art known use of the claimed combination of the phospholipids; steps a-c are obvious over the combination of Nyberg with the secondary references.

6. Claims 87-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination.

Kissel teaches a method of preparation of liposomes (lipid suspension). The method involves dissolving the phospholipid (lecithin) in methylene chloride and adding an aqueous solution of a biologically active agent, IL-2 (Example B1 on col. 13). The lipids taught include phosphatidylcholines and sphingomyelin (col. 3, lines 1-51).

Similarly Papahadjopoulos teaches a method of preparation of liposomes wherein the phospholipids are dissolved in diethyl ether and adding an aqueous solution of the active agent (example 4 and claims). Various phospholipids could be used (columns 4 and 5).

Lenk similarly teaches a method of preparation of liposomes wherein the phospholipids are dissolved in an organic solvent and adding an aqueous medium (examples and claims). The lipids used include sphingomyelin (col. 7).

Kikuchi teaches a method of preparation of liposomes wherein heated propylene glycol containing lecithin or DPPC is added with an aqueous solution. Other solvent taught is polyethylene glycol. Kikuchi further teaches sizing the liposomes using polycarbonate filters (col. 3, lines 33-46; examples and claims).

In essence, these references teach steps d and e of claim 87. Instant steps a-c in claim 87 just recite re-precipitation of the lipids used in the formation of lipid suspension. The criticality of these steps is unclear to the examiner if one is using pure phospholipids just as used in Kissel, Papahadjopoulos, Lenk and Kikuchi. Since the removal of impurities by precipitation is well-known in the art of chemistry, instant claims are deemed obvious to one of ordinary skill in the art. The reference of Nyberg which teaches selective precipitation of sphingomyelins is already of record. Applicant's claim

limitation of sterilizing filter in claim 107 is noted. However, Kikuchi teaches the filtration of the liposomes using filters and this process results in sterilization. The examiner cites in this context, the reference of Papahadjopoulos (6,210,707) which teaches liposomal suspensions are sterilized when filtered through a conventional filter (see col. 17, lines 35-44).

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that the references do not teach the preparation of lipid blend as claimed. The examiner points out that the use of pure phospholipids and their mixtures for the preparation of liposomes is clearly evident from the references and applicant has not shown that the step of precipitating the phospholipids and then re-dissolving them in a solvent prior to the addition of the aqueous medium for the preparation of liposomes is critical by direct comparison with the prior art preparation of liposomes using pure phospholipid mixtures. As pointed out above, when a phospholipid mixture is dissolved in a solvent, it is in a soluble state and this state will be no different from solution obtained by repeated precipitations of the same phospholipid mixtures. Applicant has not shown t hat the prior art lipid particles do not have the same properties as instant particles. Furthermore, applicant has not shown that one can obtain the same results using any two phospholipid mixtures.

7. Claim 117 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination as set forth above, further in view of Unger 6,416,740.

The teachings of Kissel, Papahadjopoulos, Lenk and Kikuchi have been discussed above. What is lacking in these references is the use of claimed lipid combination (DPPA, DPPE- PEG5000, and DPPC) in the preparation of the liposomes.

Such a use however, would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Unger shows that this lipid combination is routinely used for the preparation of lipospheres (examples 3 and 12).

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Kissel, Kikuchi, Papahadjopoulos and Lenk. Applicant argues that Unger fails to teach or suggest methods to make a lipid blend as claimed. The examiner points out that this reference is combined for its teachings of art known use of the claimed combination of the phospholipids.

8. Claims 87-111 and 117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Munechika (5,662,931) in combination with Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination.

Munechika discloses a method of preparation of liposomes. The method involves dissolving the lipids in an organic solvent, precipitating the lipids using a second organic solvent and hydrating the precipitate with an aqueous solution to form liposomes (col. 2, line 8 through col. 3, line 61 and examples). Munechika differs from instant method in that the precipitate is directly added to the hydrating medium instead of dissolving again in an organic solvent and adding the hydrating aqueous solution.

Kissel teaches a method of preparation of liposomes (lipid suspension). The method involves dissolving the phospholipid (lecithin) in methylene chloride and adding an aqueous solution of a biologically active agent, IL-2 (Example B1 on col. 13). The lipids taught include phosphatidylcholines and sphingomyelin (col. 3, lines 1-51).

Similarly Papahadjopoulos teaches a method of preparation of liposomes wherein the phospholipids are dissolved in diethyl ether and adding an aqueous solution of the active agent (example 4 and claims). Various phospholipids could be used (columns 4 and 5).

Lenk similarly teaches a method of preparation of liposomes wherein the phospholipids are dissolved in an organic solvent and adding an aqueous medium (examples and claims). The lipids used include sphingomyelin (col. 7).

Kikuchi teaches a method of preparation of liposomes wherein heated propylene glycol containing lecithin or DPPC is added with an aqueous solution. Other solvent taught is polyethylene glycol. Kikuchi further teaches sizing the liposomes using polycarbonate filters (col. 3, lines 33-46; examples and claims).

It would have been obvious to one of ordinary skill in the art to dissolve the precipitate containing the lipids in an organic medium again and adding the aqueous medium to this solution with a reasonable expectation of success since the references of Kissel, Papahadjopoulos, Lenk and Kikuchi all show that this method is a routinely practiced method in the preparation of liposomes.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that Munechika describes making an emulsion that includes dissolving

the lipid in a first organic solvent that is immiscible in water followed by adding a drug containing aqueous solution to the dissolved lipid and forming an emulsion. These arguments are not persuasive since instant language 'comprising' does not exclude water to form an emulsion. Munechika essentially teaches the precipitation of the lipid mixture, followed by dissolving in an organic solvent and the addition of aqueous solution. Therefore, the reference still meets the requirements of recited steps with comprising language. The Dissolving the phospholipid mixture and adding the aqueous solvent is taught by the secondary references.

9. Claims 112-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Munechika (5,662,931) in combination with Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination as set forth above, further in view of Swaerd-Nordmo (6,165,442).

The teachings of Munechika, Kissel, Papahadjopoulos, Kikuchi and Lenk have been discussed above. These references do not teach how to prepare liposomes containing ultrasound contrast agents containing perfluoropropane, that is, exchange air with perfluorohydrocarbons in a vacuum chamber.

Swaerd-Nordmo while disclosing vesicular preparations containing contrast agents teaches that the contrast agents can be incorporated by the exchanging perfluoropropane in a vacuum chamber (col. 3, Example 1). Various phospholipids which could be used are taught on col. 3, line 60 through col. 4, line 28).

It would have been obvious to one of ordinary skill in the art to use the method of Swaerd-Nordmo to encapsulate perfluoropropane in the teachings of the primary

references if the intended purpose is to use the liposomes for the delivery of ultrasound contrast agents since such a method is known in the art as taught by Swaerd-Nordmo.

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Munechika, Kissel, Papahadjopoulos, Lenk and Kikuchi. Applicant's only argument is that the addition of the teaching of Swaerd-Nordmo to the combination of the references does not teach or suggest each element of the claimed invention. This argument is not persuasive since this reference is combined for its teaching of contrast agents.

10. Claims 115-116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Munechika (5,662,931) in combination with Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination in view of Swaerd-Nordmo (6,165,442) as set forth above, further in view of Unger (6,071,495).

The teachings of Munechika, Kissel, Papahadjopoulos, Kikuchi, Lenk and Swaerd-Nordmo have been discussed above. What is lacking in these references is the final sterilization of the product. Such a sterilization however, would have been obvious to one of ordinary skill in the art if the preparation is used for human administration especially by an injection mode since sterilization of contrast agent containing liposomes by gamma-ray irradiation is known in the art as taught by Unger (6,071,495) (see col. 17, line 42 through col. 18, line 14).

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Munechika, Kissel,

Papahadjopoulos, Lenk, Kikuchi and Swaerd-Nordmo. Applicant's only argument is that the addition of the teaching of Unger to the combination of the references does not teach or suggest each element of the claimed invention. This argument is not persuasive since this reference is combined for its teaching of sterilization process and not for steps a-c.

11. Claim 117 is rejected under 35 U.S.C. 103(a) as being unpatentable over Munechika (5,662,931) in combination with Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination as set forth above, further in view of Unger 6,416,740.

The teachings of Munechika, Kissel, Papahadjopoulos, Kikuchi and Lenk have been discussed above. What is lacking in these references is the use of claimed lipid combination (DPPA, DPPE- PEG5000, and DPPC) in the preparation of the liposomes.

Such a use however, would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Unger shows that this lipid combination is routinely used for the preparation of lipospheres (examples 3 and 12).

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Munechika, Kissel, Papahadjopoulos, Lenk and Kikuchi. Applicant's only argument is that the addition of the teaching of Unger to the combination of the references does not teach or suggest each element of the claimed invention. This argument is not persuasive since this reference is combined for its teaching of the claimed combination of lipids for the liposomal preparations.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GOLLAMUDI S. KISHORE whose telephone number is (571)272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK